REMARKS

A. Summary of the Invention

Applicants' invention relates to the field of nucleic acid sequence analysis. Specifically, the invention provides methods of nucleic acid sequence analysis that use combinatorial sequence array primers to sequence and/or to detect mutations or polymorphisms within a template nucleic acid. Sequencing and/or detection are accomplished by determining a region of complementarity by use of a primer and extending the primer in order to determine that there was complementarity.

B. Summary of the Amendment

The above amendment to the specification is submitted in order to comply with 37 C.F.R. §§1.821 through 1.825. The above amendment to Claim 2 is submitted in order to define more clearly the limitations of the primer for that claim. Support for this amendment may be found on, for example, page 27, lines 32-33 of the specification. The above amendment to Claim 8 is submitted to correct a typographical error. Support for this amendment may be found on, for example, page 20, line 16 of the specification.

C. Responses to Specific Rejections

1. The Failure to Comply With 37 C.F.R. § 1.821 (a)(1) and (a)(2)

In the Office Action dated March 21, 2000, the Examiner contends that the application failed to comply with the requirements of 37 C.F.R. §1.821 through 1.825 because no submission of computer readable form sequences had been submitted. Applicants enclose herewith a paper copy of an initial Sequence Listing. SEQ. ID NOS.: 1-25 are disclosed on pages 33 - 37. Individual SEQ. ID NOS. 1-25 have been inserted into the specification by this amendment. A copy of the initial Sequence Listing in computer readable form on a 3.5 inch diskette is also enclosed herewith. The paper copy of the initial Sequence Listing inserted into the specification and the Computer readable copy of the initial Sequence Listing are identical and meet the requirements of 37 C.F.R. §§1.821 –1.825.

Therefore, Applicants respectfully submit that the amendment and the enclosed initial Sequence Listing fully satisfy the requirements of 37 C.F.R. §§1.821 –1.825.

In addition, Applicants state that the content of the paper and computer readable form are the same and, where applicable, include no new matter as required by 37 C.F.R. §1.821(e) or §1.821(f) or §1.821(g) or §1.825(b) or §1.821(d).

In view of the foregoing amendment, the enclosed substitute Sequence Listing and diskette, it is respectfully submitted that this objection is obviated.

2. The Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected Claim 2 under 35 U.S.C. §112, second paragraph as being indefinite. Specifically, the Examiner stated that it is unclear whether the word "comprises" limits the primer length or the 3-7 bases. Applicants disagree with the Examiner's position and maintain that the claim is clearly definite to one of ordinary skill in the art. Nevertheless, in order to advance prosecution, Applicants have amended the claim.

Under amended Claim 2, the primer refers to the polynucleotide sequence from which primer extension will commence. Claim 2 has been amended to reflect more clearly that the 3-7 bases refer to the length of the polynucleotide that serves as a primer, and that the primer comprises a polynucletoide. It is thus requested that the Examiner withdraw this rejection.

3. The Rejection Under 35 U.S.C. § 102(e)

The Examiner rejected Claims 1 – 27 in light of the U.S. Patent No. 5,795,714 (the "Cantor patent"). He first notes that the Cantor patent utilizes a variety of techniques for sequence analysis and points to column 6, line 38 through column 18, line 4. He then points to specific portions of the specification of the Cantor patent. Applicants respectfully submit that although the Cantor patent discloses certain techniques for sequence analysis, it does not anticipate any of pending Claims 1 – 27.

a. The Invention of the Cantor Patent

Generally, the Cantor patent describes the creation and use of a nucleic acid probe that contains a double-stranded portion and a single-stranded portion in order to determine a nucleotide sequence by positional hybridization. (Column 4, line 10 through column 5, line 53.) The Cantor patent describes a specific type of probe, as well as a specific method for using this probe, neither of which are encompassed by Applicants' claims.

According to the Cantor patent, the use of a probe that contains both a single-strand and a double-strand of DNA will allow for increased stability of the hybrid formed between the target and the probe. As the specification of the Cantor patent describes, the structure of the probe is important for the invention; it permits favorable thermodynamic conditions in large part because of the presence of the double-stranded section of the probe. (Column 7, lines 32 – 36.) Thus, the Cantor patent further discloses that following hybridization, one can determine the sequence of the target without extending the probe. The hybrization pattern can be read on an array.

The Cantor patent makes a few references to enzymatic extension of its probe, disclosing extending the portion of the probe that has been used to capture the target sequence and has hybridized to the target sequence. However, the particular enzymatic extension as disclosed in the Cantor patent is limited; it is either followed by specific types of nucleotide sequencing, such as by the Sanger or Maxam-Gilbert methods of sequencing (column 10, line 64 through column 11, line 6; column 17, line 63 through column 18, line 1) or not followed by detection and instead used for generation of new probes (column 14, lines 8-22, column 17, lines 32-47). The Cantor probes are not extended and subsequently detected for hybridization.

b. The Cantor Patent Does Not Anticipate Claim 1

In the Office Action dated March 21, 2000, the Examiner does not identify a specific portion of the Cantor patent as anticipating Claim 1. However, the Examiner does point to column 17, line 32 through column 18, line 4 and states that "an array is utilized for capture of target nucleic acid via hybridization of a complementary sequence." Because this is the first specific portion of the disclosure of the Cantor patent that the Examiner cites (other than the broad passage from column 6 through column 18), Applicants believe that the Examiner cited it in support of his position that the Cantor patent anticipates Claim 1.

This portion of the Cantor patent contains two paragraphs. The first of these two paragraphs, column 17, lines 32 – 59, describes a method for creating the Cantor probe. It discloses creating a probe that contains a single-stranded and double-stranded region. The single-stranded region is hybridized and ligated to the target. After the hybridized and ligated

target-probe complex is formed, it is enzymatically extended. The extended product is then used to create another probe.

Thus, this paragraph of the Cantor patent fails to disclose, to teach or to suggest either step (b) or step (d) of Applicants' Claim 1. Applicants' step (b) includes scanning the captured template using a primer-polymerase complex for regions of complementarity to the primer. This is not disclosed, taught or suggested by the Cantor patent, and would be inconsistent with the Cantor invention. The Cantor invention does not need a scanning step, because it requires that a stable hybrid first be formed between the target and the probe. There would be no need to scan because the portion of the Cantor probe off of which extension would occur has already hybridized to the target.

Similarly, step (d) is not disclosed, taught or suggested by this paragraph of the Cantor patent. The embodiment of this paragraph of the Cantor patent discusses the method for creating a nucleic acid probe. It does not discuss detecting an extended probe.

The second of the two paragraphs that the Examiner suggests anticipates Claim 1 (column 17, line 60 through column 18, line 4) does not supply either of the missing elements that the first paragraph is missing. It does not mention, teach or disclose a scanning step, which is included in step (b) of Applicants' Claim 1. It also does not mention, teach or suggest detection of the extended primer as included in step (d) of Claim 1.

Column 17, lines 63 –64 of the Cantor patent discusses determining the extended nucleotide sequence of the probes by Sanger dideoxynucleotide sequencing

techniques. As the Cantor patent notes, this requires taking extended nucleic acid sequences and resolving extended products by, for example, polyacrylamide gel electrophoresis. (Column 17, lines 66 - 67 though column 18, line 1.) Thus, this method disclosed by the Cantor patent would be used to reveal the sequence of the target that was not complementary to the probe, but rather adjacent to the sequence complementary to the probe. Under the Sanger method, as disclosed in the Cantor patent, (column 1, line 48 through column 2, line 5) the probe would be extended different lengths and these different lengths would be compared on a gel, giving a nucleotide sequence. However, it would not be used to provide information as to the probe itself. By contrast, Applicants' Claim 1 does not attempt to determine the sequence of the extended primer; the primer is extended solely for purposes of determining complementarity. Thus, the two paragraphs cited do not disclose, teach or suggest Applicants' invention as claimed.

For a rejection to be sustained under 35 U.S.C. § 102(e), each and every element of the claimed invention must be disclosed in the piece of prior art at issue. Because the Cantor patent does not disclose, teach or suggest all of the elements of Claim 1, it is respectfully requested that the rejection of Claim 1 based on the Cantor patent be withdrawn. Moreover, the differences between the Cantor patent that the present invention are not obvious to one skilled in the art. One skilled in the art would not look to the Cantor patent as claimed.

c. <u>The Cantor Patent Does Not Anticipate Claim 2</u>

For the reasons stated above, Applicants respectfully submit that the Cantor patent does not anticipate Claim 2 as amended.

The Examiner notes that column 12, lines 57-63 and column 17, lines 19-51 disclose various length of the components of the Cantor probes and comments that Claim 2 as filed was unclear as to what length is required. As amended, Applicants' Claim 2 further defines the primer as between 3 and 7 bases. By contrast, the passages cited by the Examiner do not describe specific lengths for the primer. Rather, they describe specific lengths for the different portions of the probe.

Because the Cantor patent does not disclose a size limit of a primer sequence, it does not anticipate Claim 2. Similarly, the Cantor patent does not render Claim 2 obvious. Thus, Applicants respectfully request that the rejection with respect to Claim 2 be withdrawn.

d. The Cantor Patent Does Not Anticipate Claim 3

Claim 3 is dependent on Claim 1. As discussed above, the Cantor patent does not anticipate or render obvious Claim 1. Thus, the Cantor patent does not anticipate Claim 3.

e. The Cantor Patent Does Not Anticipate Claims 4, 13-15 and 17.

Claims 4, 13-15 and 17 are dependant on Claim 1. As discussed above, the Cantor patent does not anticipate Claim 1. Thus, the Cantor patent does not anticipate Claims 4, 13-15 and 17.

Applicants respectfully submit that if the Examiner determines that the Cantor patent anticipates Claim 1, it still does not anticipate Claims 4, 13-15 and 17. In the Office Action dated March 21, 2000, the Examiner wrote: "It is noted that the probe/primers on the

arrays both contain a single and double-stranded region wherein the double stranded region cannot hybridize to the target but serves as the spacer of [the] instant Claim 4 and these segments serve as probes, capture reagents, allow primer, as required in instant Claims 13-15 and 17."

The Examiner does not point to a specific portion of the Cantor patent in support of the position that it anticipates Claims 4, 13-15 and 17. However, the Examiner appears to equate the Cantor probe's stabilization region with Applicants' spacer region. Applicants respectfully submit that this construction is in error. The Cantor probe's stabilization region – the double stranded region – serves to increase the stabilization of the hybrid of the template and the probe. (Column 7, lines 32-36.) By contrast, Applicants' spacer region is not designed to enhance hybridization between the primer and the template. Rather, the spacer is designed to permit the formation of a stable complex between the polymerase and the primer. This difference becomes apparent if one considers that in the Cantor patent the double-stranded region must be comprised of nucleotides, while Applicants' spacer region may be comprised of other moieties.

Claim 4 further defines the invention as to including both a capture moiety and a primer region. The Cantor patent also does not disclose both a capture moiety, and a primer region. Applicants believe that the Examiner equates the single-stranded region of the Cantor probe with both the capture moiety, and primer region. However, Claim 4 requires that these are distinct units. Thus, the Cantor patent does not anticipate Applicants' Claim 4. Because Claims 13-15 and 17 depend on Claim 4 the Cantor patent does not anticipate them.

Applicants submit that if the Examiner still determines that the Cantor patent anticipates Claim 4, Claims 13 and 14 are still not anticipated. Claim 13 and its dependent Claim 14 further define the invention by including both the capture moiety and the primer region be on separate reagents. The Cantor patent requires that a probe is one reagent. Thus, Claims 13 and 14 are not anticipated by the Cantor patent. Further, this difference would not be obvious to one skilled in the art.

f. The Cantor patent Does Not Anticipate Claims 5-12 and 16

Claims 5-12, 16, and 18-27 are all dependent on Claims 3 and 4 (which is dependent on Claim 3). As discussed above, Claims 3 and 4 are not anticipated by the Cantor patent. Thus, the Claims 5-12 and 16, which are dependent on Claims 3 and 4 are also not anticipated by the Cantor patent.

g. The Cantor patent Does Not Anticipate Claims 18-27

Claims 18-27 are dependant on Claim 1. As discussed above, the Cantor patent does not anticipate Claim 1. Thus, the Cantor patent does not anticipate Claims 18-27, which are dependent on claim 1.

Applicants respectfully submit that if the Examiner determines that the Cantor patent anticipates Claim 1, Claim 18 is still patentable over the Cantor patent. The Examiner points to the Examples and column 6, line 51 through column 9, line 50 as disclosing the various nucleotide analogues as well as labels as well as sequencing methodologies as cited in Claims 18-27. Claim 18 describes possible compositions of the spacer. The Cantor patent

does not disclose a spacer region. As discussed above, the Cantor patent only describes a stabilization region. Thus, these sections cited by the Examiner do not anticipate Claim 18.

4. The Cantor Patent and the Pease Patent do not Render Claims 1-28 Obvious

The Examiner rejected Claims 1-28 as being unpatentable over the Cantor patent in view of Pease, *et al.* (the "Pease reference"). As discussed above, the Cantor patent does not anticipate pending Claims 1-27. The missing elements described above would not be obvious to one skilled in the art. Thus, because the Cantor patents fails to teach, to disclose or to suggest elements of each of these claims, it does not render these claims obvious. Further, the Pease reference does not disclose any of the limitations missing from the Cantor patent. Thus, Claims 1-27 are patentable over the Cantor patent in light of the Pease reference.

The Examiner notes that the Cantor patent does not disclose high density arrays as included in instant Claim 28. The Examiner contends that the Pease reference at pages 5025 –5026 describes and suggests the synthesis of an increased density array, and motivates the reasonable expectation of success for the preparation and use of even higher density arrays.

Claim 28 is dependant on Claim 4, which as discussed above is patentable over the Cantor patent both alone and as noted above in combination with the Pease reference. Because Claim 4 is patentable over these pieces of prior art, Claim 28 is also patentable over these references alone and in combination. The Cantor patent's suggestion of

array practice does not disclose, teach or suggest using high density arrays. The Examiner points to column 8, lines 31-37 of the Cantor patent. However, within these paragraphs, the Cantor patent discloses "large probe arrays" not high density arrays. (Column 8, lines 55-56).

The Pease reference does not cure the infirmities of the Cantor patent as a reference against Claims 1-28. Thus, Applicants submit that the Cantor patent considered alone or in combination with the Pease reference neither discloses nor suggests the subject matter of Claims 1-28 of the subject application as amended. Further there is no motivation to combine the references. Accordingly, this rejection based on obviousness is improper and should be withdrawn.

CONCLUSION

For the reasons set forth above, it is submitted that the claims of the subject application as amended meet the standards of 35 U.S.C. Section 112, and are patentable over the art of record considered alone or in any combination. Early allowance of the application is therefore earnestly solicited.

Respectfully submitted,

Attorneys for the Applicants

by: _____

Scott D. Locke
Registration No. 44,877
Attorney for the Applicants

Telephone No. (212) 813-1600